Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/562,478	**Applicant(s)** KOSUTIC ET AL.	
	Examiner SAMUEL LIU	**Art Unit** 1656	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 5/9/11 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *6* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☒ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: *none*.
   Claim(s) objected to: *none*.
   Claim(s) rejected: *1-3*.
   Claim(s) withdrawn from consideration: *none*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☒ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). 12/28/10
13. ☒ Other: See Continuation Sheet.

/ANAND U DESAI/
Primary Examiner, Art Unit 1656

Continuation of 3. NOTE: The instant claims 1, 2 and 3 contain the new matter, i.e., the limitation "wherein the effective amount is about 20 μg/kg at least once a day", which as amended into the claims on 5/9/11, is not supported in the specification as originally filed. Although "20 μg/kg" dosage for oral administration has been describe in instant specification at page 100, lines 13-14 (where is only place the specification describe said limitation by setting forth "20 μg/kg twice a day (morning and afternoon) for 10 days"), the breadth of said "at least once a day" is broader than the "twice a day". Thus, said limitation broadens the scope of instant invention, and therefore, it is the new matter.

Continuation of 11. does NOT place the application in condition for allowance because: The 102(e) rejection of claims 1-3 are maintained because the new limitation "the effective amount is about 20 μg/kg at least once a day" set forth in said claims 1-3 has not been entered due to the above-discussed new matter issue.

The 103(a) rejections of claim 1, 2 or 3 by Russo A. F. Komarova et al. and Lee et al. are maintained because the new limitation "the effective amount is about 20 μg/kg at least once a day" set forth in claims 1, 2, or 3 has not been entered due to the above-discussed new matter issue.

The 103(a) rejection of claim 1 by Lee et al. is maintained. The response filed 5/9/11 argues that Example 4 of the lee reference does not teach a di-conjugate of salmon calcitonin (sCT) with PEG (see page 4). The response asserts that the Lee et al. teach away from instant "orally administering" the disclosed compound, the Lee' teachings "the nasal transmucosal route has advantage over the oral route" and nasal transmucosal delivery of peptides alone is significantly improved in adsorption efficiency compared with the oral administration" discourages one of ordinary skill in the art to use of the oral route (See pages 5 and 6). Thus, the response infers that a prima facie case of obviousness has not been established by the Office, and therefore request withdrawal of the rejection.

The applicants' arguments are not persuasive because, at col.7, Example 4, Lee et al. teach "PEG-sCT conjugates prepared in Examples 3 include di-PEG-sCT" (see col.9, lines 12-15), i.e., the di-conjugate contain PEG moieties at Lys11 and Lys18 residues of sCT polypeptide. The oral administration route is considered to be an alternative way for delivering sCT therapeutic. This is because the PEGylated sCT taught by Lee et al. has increased in-vivo half life span and solubility and has improved in protection from protease degradation (col.3, lines 16-19, and col.4, lines 8-11), and because Lee et al. have suggested that biologically stable peptide is suitable for oral administration (see col.7, lines 1-4). Furthermore, Lee et al. have taught possibility of modifying the current disclosure or designing other embodiments for carrying out the same purpose of the present invention (col.12, lines 44-49), wherein said "other embodiment" refers to other administration route discussed at col. 1, lines 43-48. Thus, it would have been obvious to try an administration route alternative to the nasal delivery, e.g., oral transmucosal delivery (which is convenient than nasal administration route) of the PEGylated sCT for treating pain in a patient.

Contrary to the response' assertion that liver metabolism is a hindrance to use of the oral administration (page 6, 1st paragraph, the response), the relative art teaches that PEGylated protein drugs have little toxicity, and long term PEG targeted to organs such as liver leave the body largely unchanged (see p.142, 3rd paragraph, Webster et al. (2009) PEGylated protein Drugs: Basic Science and Clinical applications, Ed. F.M. Veronese, Birkhauser Verlag, Switzerland, pages 127-146). This provided evidence that oral administration still is suitable for routing therapeutic use.

Thus, the 103 rejection is proper and maintained.

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Continuation of 13. Other: The references cited in the IDS filed 12/28/10 have been considered by Examiner.